

Emotional Arousal in Agenesis of the Corpus Callosum

Lynn K. Paul^{1,3}, Aaron Lautzenhiser², Warren S. Brown^{3,4}, Arch Hart³, Dirk Neumann¹, Michael Spezio¹ & Ralph Adolphs¹

1. California Institute of Technology, Division of Humanities and Social Sciences
2. Children's Hospital of British Columbia, Vancouver Canada
3. The Travis Research Institute, Center for Biopsychosocial Research,
Fuller Graduate School of Psychology
4. Dept. of Psychiatry & Biobehavioral Sciences, and Brain Research Institute,
University of California, Los Angeles

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Corresponding Author: Lynn K. Paul, Ph.D., California Institute of Technology, MC 228-77, Pasadena, CA 91125.

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Abstract

While the processing of verbal and psychophysiological indices of emotional arousal have been investigated extensively in relation to the left and right cerebral hemispheres, it remains poorly understood how both hemispheres normally function together to generate emotional responses to stimuli. Drawing on a unique sample of nine high-functioning subjects with complete agenesis of the corpus callosum (AgCC), we investigated this issue using standardized emotional visual stimuli. Compared to healthy controls, subjects with AgCC showed a larger variance in their cognitive ratings of valence and arousal, and an insensitivity to the emotion category of the stimuli, especially for negatively-valenced stimuli, and especially for their arousal. Despite their impaired cognitive ratings of arousal, some subjects with AgCC showed large skin-conductance responses, and in general skin-conductance responses discriminated emotion categories and correlated with stimulus arousal ratings. We suggest that largely intact right hemisphere mechanisms can support psychophysiological emotional responses, but that the lack of interhemispheric communication between the hemispheres, perhaps together with dysfunction of the anterior cingulate cortex, interferes with normal verbal ratings of arousal, a mechanism in line with some models of alexithymia.

Introduction

Patients with primary agenesis of the corpus callosum (AgCC) provide a unique opportunity to investigate the role of interhemispheric information transfer in social cognition. Primary AgCC is defined by complete absence of the corpus callosum, with minimal additional neuropathology and general cognitive functioning in the normal range (i.e. FSIQ > 80). While such individuals can still utilize crosstalk via the anterior and subcortical commissures, these are small by comparison to the 200 million or so axons that typically comprise the human corpus callosum. It is intriguing that the principal domain of deficit for these patients is in the social sphere, deficits which are typically more evident to their significant others than to the patients themselves. A small but growing body of literature has examined difficulties in social processing in individuals with primary agenesis of the corpus callosum (Brown and Paul 2000; Paul, Van Lancker et al. 2003; Paul, Schieffer et al. 2004), but the mechanisms underlying these difficulties remain essentially unknown. Social processing requires the interaction of complex cognitive skills and emotional responsiveness. The literature to date regarding primary AgCC has hypothesized that the social deficits in this group are secondary to impairments in novel complex problem solving (Brown and Paul, 2000). While there is evidence of impaired problem solving in both non-emotional tasks (Brown and Paul 2000; Schieffer, Paul et al. 2000; Garrels, Paul et al. 2001; Symington, Paul et al. 2004) and complex tasks involving emotional stimuli (Paul, Schieffer et al. 2004; Symington, Paul et al. 2004), the nature of psychophysiological responsiveness in individuals with AgCC has not been investigated to date. The current study initiates an examination of both verbal recognition of emotional arousal and autonomic psychophysiological arousal in primary AgCC using standardized emotional images from the International Affective Picture Series (Lang, 1988).

Relationship Between Social and Emotional Processes

Neurological evidence has indicated that specific structures link emotional responses and cognition. Some examples of such findings are the correlated impairments in emotional response and complex social judgment following amygdala damage (Adolphs, Tranel et al. 1998), and in emotional response and social decision-making following damage to the ventromedial prefrontal cortex (Bechara, Damasio et al. 2000). Neuroimaging studies during the deliberation of risky decisions (e.g., in financial decision-making) found activation in the ventromedial and orbital frontal cortices

(Critchley, Elliott et al. 2000; O'Doherty, Kringelbach et al. 2001). Likewise, Greene et al. (Greene, Sommerville et al. 2001) found greater activation in frontal pole, posterior cingulate gyrus, and angular gyrus, when subjects were faced with moral dilemmas that recruited strong emotional responses. A substantial recent literature has identified a network of structures that mediate between our emotional responses to stimuli, and the cognition and behavior that ensues (Adolphs 1999; Adolphs 2003).

One issue of particular importance concerns the relative specializations of the left and right cerebral hemispheres in such processing. Differentially lateralized processing has been well documented for certain functions such as language, but the roles of each hemisphere in processing emotional and social information have been much more difficult to understand. However, Ross and colleagues (Ross, Homan et al. 1994) have proposed a distinction between processing primary emotions by the right hemisphere, and socially related emotions by the left hemisphere. There are several other models of lateralized emotion processing that have been popular in the literature, which we briefly review next.

Lateralized Processing of Emotion

Historically, the right hemisphere has been thought to play a disproportionate role in emotional and social processing (Keenan, McCutcheon et al. 1999; Keenan, Nelson et al. 2001). It has been argued that the right hemisphere may contain systems for social communication that are in many ways complementary to the left hemisphere's clear specialization for language (Blonder, Burns et al. 1993). Earlier studies showed that damage to the right hemisphere can impair discrimination, recognition, and naming of emotional faces or scenes (DeKosky, Heilman et al. 1980), and suggested that the right hemisphere's role encompasses a variety of channels, including voice, face, and others (Borod 1993).

Two main theories have been put forth to elaborate on the right hemisphere's role in emotion processing: that the right hemisphere participates in processing all emotions (the "right hemisphere hypothesis"), or that the right hemisphere is relatively specialized to process negative emotions, whereas the left hemisphere is relatively specialized to process positive emotions (the "valence hypothesis") (see (Borod, Obler et al. 1998) and (Canli 1999) for reviews). To date, there has been some evidence pointing both to the right hemisphere hypothesis (e.g., (Burt and Perrett 1997; Borod, Obler et al. 1998), as well as data supporting the valence hypothesis (e.g., (Reuter-

Lorentz and Davidson 1981; Canli 1999; Lee, Meador et al. 2004), but the data are not compelling. Some modifications propose that the valence hypothesis may indeed hold for the experience and perhaps the expression of emotions, but that the perception of emotion is better described according to the right hemisphere hypothesis (Bryden 1982; Borod 1992; Canli 1999). On the other hand, there is evidence that both the perception of emotion and aspects of the experience (awareness of the details of one's feelings) rely on the same right hemisphere mechanisms (Lane, Kivley et al. 1995). There is also the related hypothesis that regions of lateral prefrontal cortex are specialized to process emotions/behaviors related to withdrawal (on the right) and approach (on the left) (Davidson 1992; Davidson and Irwin 1999).

A recent meta-analysis of 65 neuroimaging studies of emotion has led to revision of the above picture (Wager, Phan et al. 2003). The analysis found that, while there is indeed evidence for neural specialization for certain categories of emotion, dividing such specialization along the lines of "right hemisphere/ left hemisphere" is too coarse a division. Rather, there appear to be differences in processing certain emotion categories (such as approach/withdrawal) related to specific neural structures (some of which indeed may show hemispheric asymmetry).

Overall, these revisions to older views of the roles of the cerebral hemispheres in emotion processing suggest that both left and right hemispheres interact importantly in emotion processing. However, there continues to be good evidence that the right hemisphere is more involved in processing of exteroceptive emotion cues, as well as in regulating psychophysiological emotional arousal (Morrow, Vrtunski et al. 1981; Zoccolotti, Scabini et al. 1982; Tranel and Damasio 1994).

The above debates notwithstanding, it is clear that verbal labeling of emotions requires left hemisphere processing, given that language production is lateralized to the left hemisphere in the vast majority of people. One could thus envision the two hemispheres working in concert when tasks require verbal ratings of emotions, with the right hemisphere providing emotional expression and perception processing independently of language, and transfer of such processing to the left hemisphere being required in order to produce verbal descriptions and labels for the emotions.

An important finding that demonstrates the transfer of information between right and left hemispheres is an anomia for visually presented emotional facial expressions following focal damage in right posterior neocortex and white matter, despite intact facial recognition and emotional matching of the faces (Bowers and Heilman 1984;

Rapcsak, Kaszniak et al. 1989; Rapcsak, Comer et al. 1993). Given the selective emotional anomia found in these subjects, it appears unlikely that their impairment resulted from a general defect in recognizing the emotion, or a general defect in naming ability (although it should be noted that processing emotional speech content indeed appears to rely more on the right than the left hemisphere (Borod, Andelman et al. 1992; Borod, Rorie et al. 2000). Instead, it is plausible that these patients suffered from a disconnection between, on the one hand, information in right posterior cortices about the emotion shown in the face, and, on the other hand, the left hemisphere networks required for lexical retrieval of the name of the emotion. If we speculatively extend these findings to a similar disconnection that is of a larger scale, as would be the case in primary callosal agenesis, they could account for an inability to verbalize emotional information generally despite intact physiological regulation to emotional stimuli.

The attempt to localize social and emotional information processing to the left or the right hemisphere tends to ignore the fact that the processing is likely to draw on both hemispheres working in concert, and on a distributed set of many neural structures working together (some of which may be more important on the left, whereas others of which may be more important on the right). Relatively little attention has been paid to the issue of interhemispheric connectivity, compared to the localization of function within each hemisphere.

Cognitive Functioning in AgCC

The predominance of the literature on AgCC concerns its neurocognitive and clinical aspects, only recently has research been conducted that examines the social processes in multiple-subject studies of primary AgCC. Brown and Paul (2000) define Primary AgCC (called Primary ACC in that paper) as the condition of complete callosal agenesis, with IQ at or above normal range and minimal unrelated neuropathology. Although intellectual disabilities are often associated with AgCC in the context of other syndromes and diseases (for example, Andermann Syndrome, Aicardi Syndrome, Fetal Alcohol Syndrome), AgCC may also be found in individuals with normal-range IQs (Chiarello 1980). However, even when IQ is normal and there is no gross indication of cognitive deficit, more subtle deficits are still apparent (Sauerwein, Nolin et al. 1994). Most notably, individuals with AgCC and normal intelligence have been shown to exhibit deficits in certain interhemispheric transfer (IHT) tasks (Fischer, Ryan et al. 1992;

Sauerwein, Nolin et al. 1994; Dunn, Paul et al. 2000), bimanual coordination (Jeeves, Silver et al. 1988; Sauerwein, Nolin et al. 1994) and the bilateral comparison of complex visual stimuli (Brown, Jeeves et al. 1999).

Individuals with AgCC also show specific difficulties with higher cognitive functions, such as complex spatial memory deficits (Temple and Ilesley 1994), deficits in concept formation and problem solving (Schieffer, Paul et al. 2000), and difficulties in their ability to learn from feedback, strategize, and imagine consequences for their actions (Symington, Paul et al. 2004). Language deficits have also been found: individuals with AgCC are impaired in phonemic discrimination (Temple and Ilesley 1994), phonological reading (Temple, Jeeves et al. 1989; Temple, Jeeves et al. 1990), as well as in the processing and use of nonliteral language (Paul, Van Lancker et al. 2003; Brown, Symington et al. 2005). For example, individuals with AgCC often offer “meaningless” or “out-of-place” comments during normal conversation (O'Brien 1994), and have a tendency to “miss the point” of stories and jokes (Brown, Paul et al. 2005). Finally, difficulties in the recognition of vocal prosody have also been noted (Paul, Van Lancker et al. 2003). While deficits in complex problem solving and paralinguistic processing are evident using specialized research methods to examine individuals with AgCC, they are most commonly noticed through their impact on the social skills of these individuals.

Social and Emotional Functioning in AgCC

Arguably the most complex domain of reasoning and problem solving in human functioning is that of social cognition. It is also the domain that is most directly impacted by emotional processing. The social deficits in primary AgCC are of critical concern to the family members of these individuals. Despite their intact general intelligence, most adults with AgCC whom we have studied have serious difficulty maintaining jobs and establishing relationships outside of their family due to their social impairments. Specifically, research has documented that individuals with AgCC have poor social insight and peer relationships (Paul 1998; Brown and Paul 2000), poor social problem solving and social judgment (Stickles, Schilmoeller et al. 2002; Symington, Paul et al. 2004), impaired theory of mind (Symington, Paul et al. 2004), and an inadequate understanding of pictures portraying complex social interactions (Turk, Khatchikian et al. 2003; Paul, Schieffer et al. 2004).

The latter studies utilized stimuli from the Thematic Apperception Test (TAT) to examine participants' ability to generate logical, socially complex, and socially relevant stories. The study by Paul et al (2004) found that blind-raters (clinical psychologists highly familiar with the TAT) consistently ranked AgCC subjects worse than controls on each of these rating categories (logic, social complexity, and social relevance to the picture). Turk et al (2003) examined these stories (with the addition of a few more AgCC subjects) using semantic analysis and found that adults with AgCC used fewer emotion words than age and IQ matched controls. This suggests that while individuals with AgCC may have impoverished story-telling due to limitations in complex processing (poor logic of the stories), they are also deficient in identifying the emotional themes of the cards.

AgCC and Psychophysiology

A possible explanation for the lack of spontaneously generated emotional content to the TAT is that individuals with AgCC may have a decreased psychophysiological response to emotionally laden stimuli. If emotional arousal is not present or is diminished in these individuals, then that would at least in part explain their emotionally impoverished stories.

Autonomic nervous system response is a well-validated way of assessing emotional reactivity (Davidson 1993). The most commonly used method of measurement and quantification of autonomic arousal is the skin conductance response or SCR) (Cacioppo and Tassinary 1990). Various stimuli can be used to evoke reliable ratings of emotion as well as reliable psychophysiological responses. Possibly the best validated set are the International Affective Picture System (IAPS), a collection of 600 pictures developed by Peter Lang and colleagues (Lang, Oehman et al. 1988) for the National Institute of Mental Health (NIMH). It is based on a three-dimensional view of emotional response: affective valence (pleasantness versus unpleasantness), arousal (excited versus calm), and dominance/control. The pictures for the IAPS were chosen by Lang et al. such as to "fill all portions of [this] affective space" (Lang et al., p. 2). Normative ratings for each picture along the three dimensions were developed for both adults and children.

(Lang, Greenwald et al. 1993) presented a set of 42 IAPS slides to a group of undergraduate students while collecting facial EMG and SCR data and verbal ratings. SCR was found to monotonically increase with ratings of arousal. Furthermore, they did

not find skin conductance change to be related to emotional valence, supporting the theory expressed by (Lang 1995) that arousal and valence are distinct dimensions.

The IAPS have also been used extensively in investigations of emotion dysfunction. In a one study, (Fitzgibbons and Simons 1992) used psychophysiological responses and verbal ratings to a set of 21 IAPS slides to differentiate between individuals with anhedonia (the inability to experience pleasure) and normal controls. With respect to verbal ratings, they found that individuals with anhedonia reported a less positive response (affective valence) to both positive and aversive stimuli than normal controls. No difference was found with respect to ratings of arousal. With respect to SCR, there was an increased SCR with higher-arousal slides for both groups.

Aims of the present study

In this study, selected stimuli from the series were used to investigate emotional response (both psychophysiological and verbal responses) in individuals with AgCC and matched healthy controls. Based on the observed psychosocial deficits in AgCC, including anecdotes of often labile emotions in social interactions and evidence of diminished use of emotion words in TAT stories, it was expected that subjects with AgCC would exhibit relatively intact SCR responses to IAPS slides, but give relatively insensitive ratings of arousal and valence. That is, while our study was rather exploratory in nature, our general hypothesis was that explicit ratings of emotion would be relatively impaired, whereas implicit emotional responses such as SCR would be relatively intact in subjects with AgCC.

Materials and Methods

Participants

An initial 11 individuals with complete agenesis of the corpus callosum (AgCC) and 12 normal controls (NC) completed the experiment. We included only NC participants who had completed a high school degree (or equivalent), had no history of head injury, psychiatric diagnosis or learning disabilities, and reported no current drug abuse. Inclusionary criteria for participants with AgCC were complete absence of the corpus callosum as evident in MR scans of each subject's brain (see Fig. 1 for an example), a FSIQ of 80 or greater, no history of head injury, no major medical conditions other than AgCC, no psychiatric diagnosis, limited other significant neuropathology, and no current or past history of drug abuse. Due to greater than typical frequency of left-handedness in AgCC population, both right and left-handed individuals were included. We did not exclude subjects with additional structural abnormalities that are generally co-occurring with AgCC and considered to be cognitively benign (colpocephaly—all subjects; small cysts in area where corpus callosum would be located—2 subjects; small region of heterotopic gray matter in left frontal region —1 subject). We subsequently excluded 2 participants with AgCC due to failure to comply with the instructions during the experiment. Consequently, 3 NC participants were excluded from the final data analysis so as to best match groups on age and IQ. The final group consisted of 18 participants (9 NC and 9 AgCC) that were statistically matched using student's t-tests for age (AgCC mean = 28.22, sd = 6.83, range 19 - 37; NC mean = 24.00, sd = 5.92, range 18 – 34; t-test = 1.40, df = 16, p = .18) and FSIQ (AgCC mean = 96.00, sd = 6.61, range = 91 - 105; NC mean = 98.00, sd = 5.87, range = 88 – 104: t = -.67, df = 16, p = .51); see Table 1. Of the subjects with AgCC, 7 were male and 2 female, with two males left-handed. In the NC group, there were 8 males and 1 female, all right handed.

The 9 participants with AgCC were part of a larger study of cognition and psychosocial processing conducted in the laboratory of Warren Brown, Ph.D. All of the subjects have participated in studies cited in the background section of this paper and their IHT deficits and psychosocial profiles are reflected by the description provided through those studies. All of these subjects with AgCC have had difficulty keeping employment due to their poor problem solving and social skills. Those who have held steady employment (3 participants) have been in highly supportive work environments with minimal stress. Two of the participants are married, both living in close proximity to

extended family that assist them in the relationship. The others have all had unsuccessful relationships characterized by the participants with AgCC deficits in theory of mind as evidenced by frequent conflict with poor insight regarding the perspective of their partner and often being taken-advantage-of (financially and physically) by the partner due to gullibility. Significant others report that these individuals have emotional outbursts that are very short-lived and about which they express minimal insight. Discussion of emotions with these participants tends to be very childlike and often seems more rehearsed than genuine. These participants have very few if any friendships apart from family ties and all experienced being teased and isolated as children. Due to evidence that the right hemisphere is critical for emotional processing, we estimated the right hemisphere functioning of these AgCC subjects using PIQ. For this group, PIQ was within average to above average range for all subjects (AgCC mean PIQ = 101.55, sd = 10.39, range 87 -119 with only one subject PIQ below 95).

Stimuli

We chose 15 target stimuli, divided into positive, aversive, and neutral categories according to normative valence ratings (Lang, 1997). 14 pictures from the IAPS and 1 from L. M. (Lautzenhiser 2003) were so as to span a range of valence and arousal ratings, but avoided stimuli that could upset subjects (e.g., due to the disturbing nature of the images, we did not include sexual images or mutilations, the stimuli that normally receive highest possible arousal ratings) (Table 2). The positive stimulus taken from Lautzenhiser's dissertation (2003) was used because she found that it elicited robust SCR in anhedonic children (the focus of her study). The normative valence ratings for the IAPS slides were compared between the three stimulus groups using a one-way ANOVA revealing highly significant difference between stimulus groups $F(2,11) = 47.28$, $p < .001$ (Valence means: positive 7.39 (.70), aversive 3.26 (.43), neutral 4.91 (.07)). Normative arousal ratings were compared for the positive and aversive stimuli only, revealing significantly higher arousal ratings for the aversive stimulus group $F(1,8) = 6.76$, $p < .05$ (Arousal means: positive 4.75 (.68), aversive 6.27 (1.1)).

Stimuli were presented in the following fixed manner for every subject:

1. 5 second nonstimulus slide that read, "please relax, The slide will appear in about 5 seconds."
2. 5 second presentation of IAPS stimulus slide
3. 5 second nonstimulus slide that read, "please continue to relax."

4. Rating slide stating, “now complete the slide ratings” remained up until ratings were completed.

Procedure

All participants gave written informed consent. Silver finger electrodes and conductive gel were placed on the middle segment of the index, middle, and ring fingers of the left hand, with the ground electrode placed on the middle finger. Following electrode placement, the examiner explained the use of the SAM rating system.

Stimuli were displayed on a 17-inch computer screen, five feet in front of the participant, in a normally lit room. During stimulus presentation, one experimenter sat in front and to the left of the participant and read the experiment instructions, collected behavioral observations during the experiment, manually recorded the participant ratings, and clarified participant questions when needed. This examiner was seated to the left due to the configuration of the testing room, a position which allowed for the least visual interference between the subject and the stimuli. A second experimenter operated the computer used for SCR recording, which was situated behind the participant. This experimenter controlled the initiation and termination of the stimulus presentation sequences, entered participant ratings into the computer, and monitored real-time SCR readings. SCR was recorded with an Autogen model 3400 Biofeedback monitor. The self-balancing analog output of the Autogen 3400 was fed to the data-gathering computer. SCR data were gathered at a rate of 18 samples per second. The data were subsequently detrended and peak response amplitudes were calculated using the difference between a 5-second pre-stimulus window and a 5-second post-stimulus window. We included in our analysis only trials on which SCR activity of some kind was evident, and discarded those on which no apparent signal could be discerned. This resulted in discarding about a quarter of the trials from the subjects with AgCC due to insufficient signal-to-noise. Due to technical problems, we were unable to obtain usable SCR data from the control subjects in this experiment, and also from 2 of the subjects with AgCC (A32 and A33). The SCR data are thus limited to 7 of the subjects with AgCC.

Participants were asked to rate stimuli using a modified form of the IAPS SAM rating system on 2 dimensions: happy versus unhappy rating (valence) and excited versus calm (arousal) on 5-point scales. The standard 9-point SAM scale was simplified

to 5 point to minimize cognitive complexity of the task. Ratings were then converted back to the 9-point scale for comparison with Lang et al (1997) normative ratings. It should be noted that the AgCC subjects included in this paper also participated in the study by S. Symington et al. (2005) where they were able to produce normal ratings on simple theory of mind tasks, thus indicating that the ability to give cognitive ratings *per se* was not impaired in our subjects.

Results

We collected both verbal ratings of arousal and valence for the stimuli, as well as skin-conductance response. The ratings were analyzed with 2 (AgCC, control) x 3 (pleasant, aversive, neutral stimuli) ANOVAs separately for arousal and for valence. The skin-conductance responses were analyzed using resampling statistics.

Ratings of Valence and Arousal

As Figure 2 shows, subjects with AgCC gave valence ratings that were less specific and showed a larger variance. While mean ratings were in the same direction as those of controls, some individuals with AgCC gave highly unusual ratings that were never given by any control. The large variance shown by subjects with AgCC produced the effect that their mean ratings for pleasant (0.71 (0.95)) and aversive (-0.21 (0.96)) stimulus classes were closer to those of the neutral stimuli (0.03 (0.42)) compared to those given by controls (pleasant: 1.40 (0.32); aversive: -0.89 (0.50); neutral: -0.08 (0.22), means and S.D.s). There were no specific individuals responsible for the effect across stimulus categories: those that gave highly abnormal ratings for some stimuli, gave normal ratings for others.

A similar effect was seen for arousal ratings (Fig. 2). Mean arousal ratings given by subjects with AgCC were lower for pleasant (2.24 (0.71)) and aversive stimuli (2.0 (0.97)) but somewhat higher for neutral stimuli (1.81 (0.54)), compared to those given by controls (pleasant: 2.73 (0.67); aversive: 3.0 (0.33); neutral: 1.1 (0.78)).

These ratings were examined with 2x3 ANOVAs separately for the valence and the arousal ratings, using each subject's mean rating across all stimuli within a category as the dependent measure. For valence, there was a significant effect of emotion category ($F(2,48)=30.5$, $p<0.0001$) but not subject group ($F(1,48)=0.04$, n.s.), as well as a significant interaction ($F(2,48)=5.3$, $p<0.01$). Post-hoc Scheffe-corrected t-tests showed trends for ratings given by subjects with AgCC being abnormally low for

pleasant stimuli, and abnormally high for aversive stimuli ($P_s < 0.1$), compared with control ratings, consistent with Figure 2.

For arousal, there was an effect of emotion ($F(2,48)=15.2$, $p<0.0001$) but none of group ($F(1,48)=2.0$, n.s.), with an interaction ($F(2,48)=8.3$, $p<0.001$). Scheffe-corrected post-hoc t-tests showed that subjects with AgCC gave significantly lower arousal ratings for aversive stimuli (difference: 1.1 (0.33 SEM), $p<0.01$).

The above analyses examine differences between subject groups across classes of stimuli, using mean ratings given by each individual subject within a group as the dependent measure. A complementary analysis examined the mean ratings given across subjects within a group, for each individual stimulus shown. As Figure 3A shows, such an analysis for valence reveals that even though subjects with AgCC gave ratings closer to neutral for all stimuli (the slope of the regression line of AgCC versus control ratings is less than 1), their ratings still discriminated amongst different stimuli in a way similar to the discrimination seen in controls (the correlation of ratings given by subjects with AgCC with control ratings was 0.87, Spearman rank-order correlation). Similarly, Figure 3B shows that arousal ratings are highly attenuated in subjects with AgCC (the slope of the regression line is very flat), although there is a correlation between ratings given by subjects with AgCC and those given by controls (Spearman's $R = 0.50$).

Arousal and valence ratings for each group (AgCC and NC) were correlated also with the published normative IAPS ratings, with controls showing higher correlation on both ratings (valence: 0.61 for subjects with AgCC and 0.83 for controls; arousal: 0.22 for subjects with AgCC and 0.76 for controls).

Skin Conductance Responses:

While the manner in which SCR was measured in the subjects with AgCC precludes an absolute analysis relative to a calibrated value, and while therefore we are unable to compare them quantitatively to the SCRs that might be given by healthy individuals, we can make some preliminary observations about these responses. Subjects with AgCC certainly did on occasion produce large, convincing responses evoked by the stimuli (Figure 4). Moreover, their SCRs on average discriminated highly arousing stimulus categories from neutral: SCRs were higher for pleasant and aversive stimuli than for neutral stimuli (Figure 4). Given the sparse and non-normally distributed

data, and the large variance in the AgCC subjects, we assessed the statistical significance of these findings using resampling. Using 10,000 bootstrap replicates, we found that SCR responses to positive slides differed significantly from SCR responses to neutral slides ($P < 0.03$; 95% confidence interval of the difference of the means: 1.29, 22.82) and that SCR responses to aversive slides were marginally different from SCR responses to neutral slides ($P < 0.07$; 95% CI: -0.99, 11.61). Future studies in which responses can be directly compared between AgCC subjects and control subjects will be required to determine whether these responses are in fact entirely normal or not, but they do demonstrate SCR discrimination of emotion categories.

A further preliminary analysis examined, for each subject, the correlations between SCR and cognitive ratings. There was no correlation between SCR and either subjects' own valence ratings or normative valence ratings (mean R s between 0 and 0.1), but there was a weak correlation with both subjects' own arousal ratings as well as normative arousal ratings (R s of 0.24 and 0.23, respectively). This correlation strengthened when one included only the data from those subjects with AgCC whose SCR responses discriminated pleasant or aversive stimuli from neutral in the first place (4 out of the 7 patients; resulting R s: 0.47, 0.34).

Discussion

Using stimuli from the IAPS we found that the group of subjects with AgCC contrasted with healthy controls as follows:

1. Their cognitive ratings showed a larger variance, for both valence and arousal.
2. Ratings of arousal were general lower, especially for aversive stimuli, and ratings of valence closer to neutral.
3. Skin-conductance responses were nonetheless evoked by the stimuli, and showed differences between stimulus categories, although it remains to be examined how normal these in fact were.

Taken together, the findings indicate that AgCC results in a relatively spared ability to generate psychophysiological emotional responses with a relatively compromised ability to produce cognitive ratings.

Caveats

It is important to note several caveats to the present study. One methodological shortcoming was already noted above: our skin-conductance data, while demonstrating psychophysiological responsivity in subjects with AgCC, do not demonstrate that such responsivity was entirely normal, since no comparison with controls was possible. Nonetheless, subjects with AgCC clearly are able to trigger large skin-conductance responses to some stimuli (e.g., Fig. 4B), and emotion categories were discriminated by the SCR responses.

It is also important to note that further control tasks would be required in order to conclude that the impaired emotion ratings we report are specific to rating emotion. While our AgCC subjects did not have a general impairment in giving ratings as such (cf. Methods), as also borne out by their more disordered ratings for arousal than for valence, it may well be that they would be impaired at giving other complex social ratings. Of course, such a finding could well be consistent with the possibility that the emotion rating itself is the primary deficit; but it also remains possible that we are instead

tapping into a more complex disability in appreciating complex social material, and that the abnormal emotion ratings we report are themselves a consequent of that deficit.

A third important point is that the group of subjects with AgCC, while sharing in common callosal agenesis, are quite variable in other respects. Their anatomical MR scans show considerable variation in other structural respects; it is therefore perhaps not particularly surprising that the variance in their data is also considerable (e.g., Fig.2). Although our statistical analyses and data summaries treat the group of subjects, we believe it is important to emphasize their individual differences. A multiple case-study approach in which the details of structural and/or functional neurobiological data for each subject are taken into account may well be more elucidating in the future, and such studies are currently underway in our laboratory.

Implications for alexithymia

Studies of surgically commissurotomed patients (who, unlike patients with AgCC, have adult-onset disconnection of the hemispheres) have suggested a deficit in socioemotional function often diagnosed as alexithymia, an inability to verbally describe one's feelings or moods (Nemiah and Sifneos 1970; Sifneos 1972). (TenHouten, Hoppe et al. 1986) performed a lexical analysis of subjects' verbal descriptions to emotionally charged films, and found evidence that commissurotomed patients showed more evidence of alexithymia. A number of other studies have supported the "functional commissurotomy" theory of alexithymia, according to which functional (or actual anatomical) disconnection between the hemispheres would be one cause of, or contribute to, alexithymia (Zeitlin, Lane et al. 1989; Parker, Neightley et al. 1999; Lumley and Snelky 2000; Grabe, Moller et al. 2004; Tabibnia and Zaidel 2005). It is therefore of interest to consider the present findings in relation to this idea.

The IAPS has been used in a landmark investigation of EMG and SCR responses in alexithymia. (Roedema and Simons 1999), studying college students, collected the subjective ratings, facial EMG, and SCR response to 21 IAPS slides of 34 subjects with alexithymia (as defined by scores on the Toronto Alexithymia Scale) and 31 normal controls. Results indicated that individuals with alexithymia evidenced significantly fewer SCR responses than did the normal controls, although no significant difference was noted in terms of the magnitude of SCR responses. With respect to verbal ratings, range of arousal ratings reported by individuals with alexithymia was

restricted as compared to the normal controls. No such difference was found with respect to ratings of valence.

The present data in subjects with AgCC bear some similarity to the classic study of Roedema and Simons (1999). Some other data provide further support for the idea that these subjects have a form of alexithymia. Another study found that subjects with AgCC with normal-range IQ are impoverished in the stories they tell to picture cards from the Thematic Apprehension Test (TAT). Compared to the stories of IQ-matched controls, the stories of the individuals with AgCC consistently ranked lowest on logic, narrative content, and social understanding (Paul, Schieffer et al. 2004). Using a content analysis program to assess for thematic differences, (Turk, Khatchikian et al. 2003) analyzed the stories to six TAT cards and found that, compared to IQ-matched controls, individuals with AgCC gave simplistic, concrete, nonemotional responses to the TAT cards, and used fewer words that could be classified by the analysis program into emotional categories. It will be important to assess alexithymia directly in subjects with AgCC in future studies.

One instrument that could provide further insight is the Levels of Emotional Awareness Scale (LEAS) developed by Richard Lane (Lane, Kivley et al. 1995). Functional neuroimaging studies have demonstrated that the degree to which subjects are aware of their emotions, as assessed by the LEAS, correlates with the degree of right hemisphere activation (Lane, Kivley et al. 1995). Another important brain structure whose activation correlates with the LEAS is the dorsal anterior cingulate cortex (Lane, Reiman et al. 1998; Lane 2000). This region is especially interesting in the present context, given that subjects with AgCC show unusual folding of the cingulate gyrus, such that it is in fact unclear whether or not they have an equivalent anatomical (or functional) region at all. Lane has proposed that alexithymia due to anterior cingulate dysfunction arises from something like a deficit in attention to one's own feelings, consistent with the known role of this region in attentional processing (Lane, Fink et al. 1997; Lane, Reiman et al. 1998; Lane 2000). This idea would suggest that individuals with AgCC may not attend normally to emotional stimuli. If psychophysiological reactivity is relatively independent of attention, whereas cognitive recognition, ratings, and elaboration are relatively dependent on it, this could explain the pattern of relatively preserved SCR but blunted emotional ratings and impoverished TAT stories seen in AgCC. A further question that therefore needs to be investigated is whether, or to what extent, deficits in

emotion processing seen in these subjects results from dysfunction (or absence) of the anterior cingulate cortex, in addition to (or rather than) their callosal agenesis.

Further along these lines, it is clear that congenital absence of the corpus callosum results in a variety of structural and functional brain abnormalities, above and beyond the mere absence of the corpus callosum itself. One structural (and presumably functional) aspect is the abnormal cingulate cortex mentioned above, but it is highly likely that other structures are also anatomically and functionally abnormal. For instance, one could posit a disconnection between processing of conceptual knowledge about emotion categories (e.g., in dorsolateral prefrontal cortex) from representations of the somatic changes that constitute those emotions (e.g., in somatosensory/insular cortices). Furthermore, it should be borne in mind that other commissural connections are still intact in AgCC and could provide an anatomical substrate for bihemispheric processing of emotion. Ultimately, we would want to understand what it is about the entire system of structures that participates in processing emotionally and socially relevant information that is disordered in AgCC, a large question that will ultimately require detailed anatomical and functional brain imaging to accompany the behavioral data such as we report here.

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Table 1

Demographics for AgCC Participants

| ID | <i>IQ</i> | <i>Age</i> | <i>Handedness</i> | <i>Gender</i> | Education | <i>Other neuropathology</i> |
|-----|-----------|------------|-------------------|---------------|-----------|---|
| A1 | 105 | 21 | R | M | 13 | None |
| A2 | 87 | 27 | L | M | 12 | Cortical dysplasia, heterotopic grey matter |
| A3 | 97 | 19 | L | M | 12 | Interhemispheric cyst |
| A5 | 91 | 30 | R | M | 12 | Interhemispheric cyst |
| A7 | 102 | 31 | R | M | 14 | None |
| A32 | 90 | 37 | R | F | 12 | None |
| A33 | 91 | 34 | R | M | 12 | None |
| A36 | 97 | 20 | R | F | 12 | None |
| A45 | 104 | 35 | R | M | 12 | None |

Table 2*Slides in Order of Presentation*

| Slide description | Lang's number | Slide-type | Normative valence ^a | Normative arousal ^a |
|-------------------|------------------|------------|-----------------------------------|-----------------------------------|
| Basket | 7010 | Neutral | 4.94 (1.07) | 1.76 (1.48) |
| Diver and shark | 5622 | Positive | 6.33 (1.78) | 5.34 (1.96) |
| Puppy with tie | N/A | Positive | N/A | N/A |
| Snake | 1120 | Aversive | 3.79 (1.93) | 6.93 (1.68) |
| Dustpan | 7040 | Neutral | 4.69 (1.09) | 2.69 (1.93) |
| Butterfly | 1603 | Positive | 6.90 (1.48) | 3.37 (2.20) |
| French fries | 7460 | Positive | 6.81 (2.08) | 5.12 (2.49) |
| Dentist | 3280 | Aversive | 3.72 (1.89) | 5.39 (2.38) |
| Fork | 7080 | Neutral | 5.27 (1.09) | 2.32 (1.84) |
| Ice cream | 7330 | Positive | 7.69 (1.84) | 5.14 (2.58) |
| Bunnies | 1750 | Positive | 8.28 (1.07) | 4.10 (2.31) |
| Gun | 6230 | Aversive | 2.37 (1.57) | 7.35 (2.01) |
| Umbrella | 7150 | Neutral | 4.72 (1.00) | 2.61 (1.76) |
| Roaches | 1274 | Aversive | 3.17 (1.53) | 5.39 (2.39) |
| Puppies | 1710 | Positive | 8.34 (1.12) | 5.41 (2.34) |

^aFrom Lang, Bradley, and Cuthbert (1997).

Figures

Fig. 1

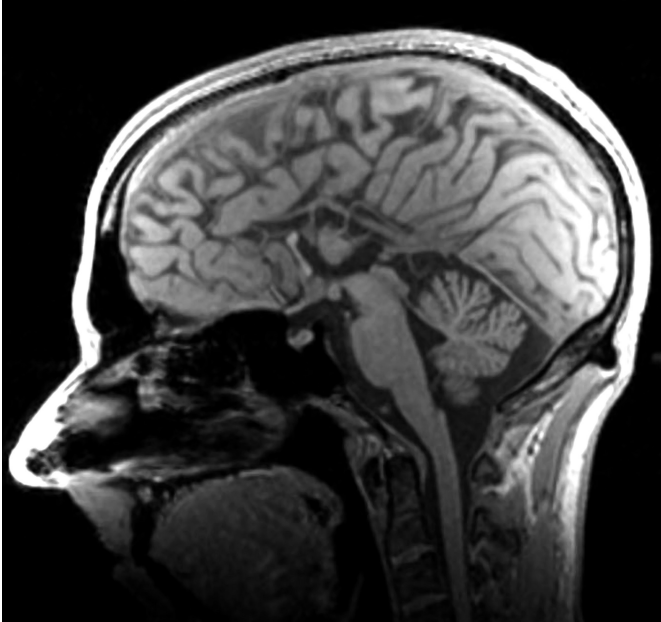


Figure 1 legend: T1-weighted structural sagittal MR scan of the brains of one of the subjects with AgCC (subject A1) demonstrating complete absence of the corpus callosum. In addition, evident are gross structural abnormalities in the appearance of gyri and sulci, which are a consequence of the congenital absence of the callosum and which are quite variable from subject to subject.

Fig. 2

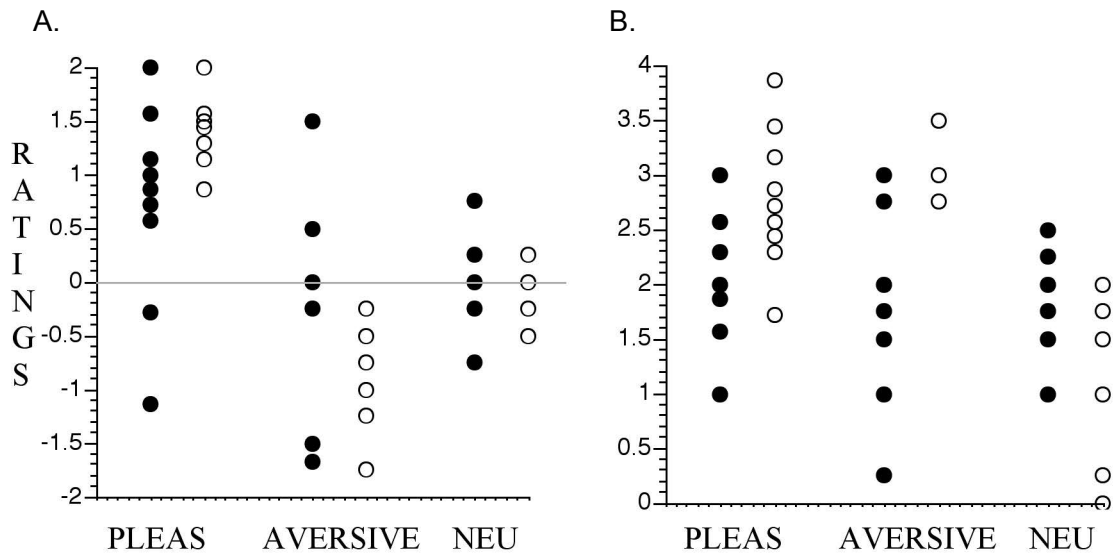


Figure 2 Legend: Ratings of Valence (A.) and arousal (B.). Mean ratings given by each subject to the class of stimuli are indicated by the datapoints. Five-point scales were used for both valence (negative: unpleasant, positive: pleasant, zero was stated to be neutral valence) and arousal (2 was stated to be an average, neutral level of arousal, less than two more relaxed than average, and above two more aroused than average). Filled circles: subjects with AgCC; open circles: controls.

Fig. 3

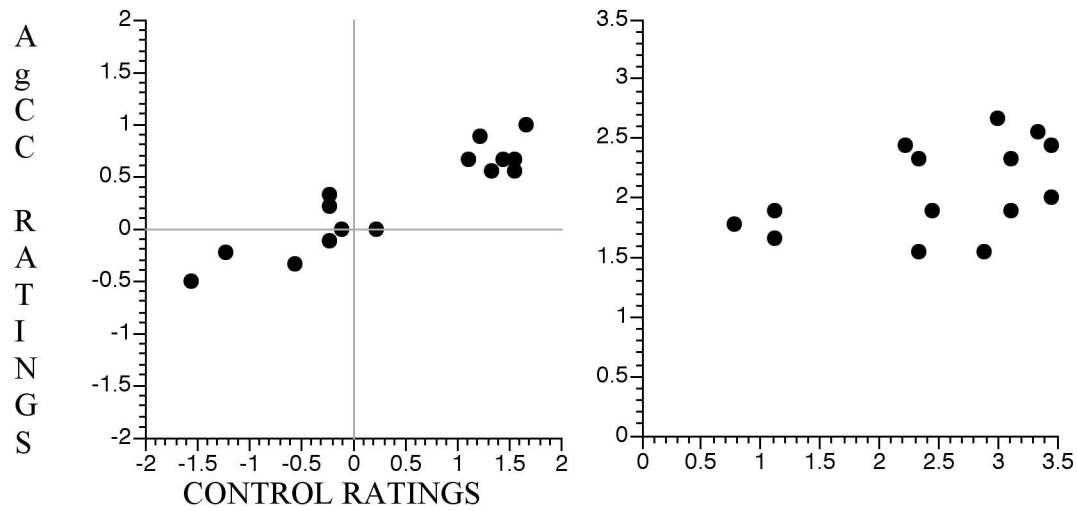


Figure 3 legend: Correlations between ratings for each of the 15 individual stimuli given by AgCC subjects and by controls. Shown are ratings for valence (A.) and arousal (B.) given by subjects with AgCC (y axes) and by controls (x axes). Compared to control ratings, those given by subjects with AgCC have a compressed range (slope is less than 1), but are correlated.

Fig. 4.

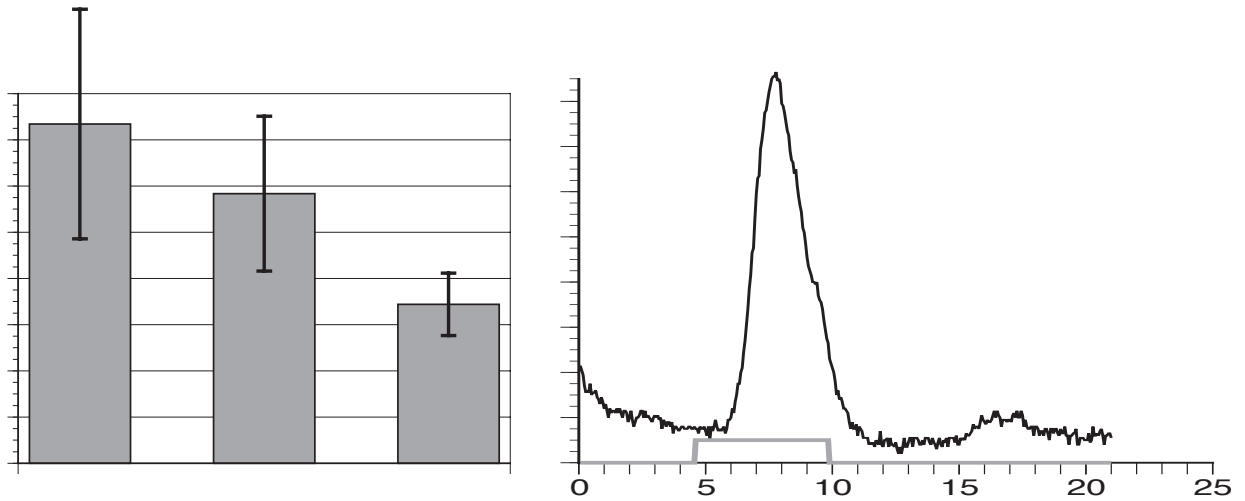


Figure 4 legend. Skin conductance responses in subjects with AgCC. Shown are mean (and SEM) amplitudes of SCR responses given by 7 subjects with AgCC to each of the stimulus categories (left). An example of an evoked SCR (in response to one of the pleasant slides, puppies) is shown on the right (grey bottom trace indicates presentation of the stimulus). Y-axis units measure the amplitude of the skin conductance, in uncalibrated microsiemens.